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EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/994,585	Applicant(s) LEVINSON, DOUGLAS	
	Examiner Jon D. Epperson	Art Unit 1639	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,15,51,66 and 81-150* is/are pending in the application.

4a) Of the above claim(s) *1,15,51,66,132-141 and 143-149* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *81-131,142 and 150* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1/1

DETAILED ACTION

Status of the Application

1. The Supplemental Response filed October 4, 2004 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 1-80 were pending. Applicants canceled claims 2-14, 16-50, 52-65 and 67-80. In addition, Applicants added claims 81-150 and amended claims. Therefore, claims 1, 15, 51, 66 and 81-151 are pending in the present application.

4. Claims 1, 15, 51, 66, 132-141, 143-149 are drawn to non-elected species and/or inventions and thus these claims are/remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim.

5. Therefore, claims 81-131, 142 and 150 are examined on the merits in this action.

IDS

6. The information disclosure statement filed May 17, 2004, fails, in part, to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because several publications cited therein (e.g., ID, LD, QD, TD, etc), lack publication dates and/or page numbers, which are necessary

elements for consideration. While the other patent and other publications cited therein, and supplied, therewith, have been considered as to the merits, these publications have not. Applicant is advised that the date of any re-submission of these citations contained in this information disclosure statement or the submission of the missing element – their publication dates – will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPE § 609 C(1).

Priority

7. The Examiner notes that Applicants' petition to accept an unintentionally delayed claim of priority (e.g., see 3/4/04 submission) was recently granted (e.g., see 3/9/05 Response). However, Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 120 as follows:

This application claims benefit to 60/253,629 (filed 11/28/2000) and is a CIP of 09/756,092 (filed 1/8/01), which claims benefit of 60/175,047 (filed 1/7/2000) and claims benefit of 60/196,821 (filed 4/13/2000) and claims benefit of 60/221,539 (filed 7/28/2000). The application is also a CIP of PCT/US01/00531 (filed 1/8/2001), which claims benefit of 60/175,047 (filed 1/7/2000) and claims benefit of 60/196,821 (filed 4/13/2000) and claims benefit of 60/221,539 (filed 7/28/2000). However, the CIP applications upon which priority is based and their related provisional applications fail to provide adequate support under 35 U.S.C. § 112 for the claims of this application. Specifically, the Examiner cannot find support for the new subgenus of "disease causing" substances. If applicant believes this to be in error,

applicant must disclose where in all of the priority documents that this "disease causes" subgenus can be found.

The Examiner further notes that if the written description of a priority document does not use precisely the same terms as used in the current claims (e.g., "disease causing" substances), the question then turns to whether the priority documents to which priority is sought directs or guides one of skill in the art to the subject matter that is currently claimed (e.g., see, *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) ("In the absence of blazemarks [that the claimed compounds were of special interest], simply describing a large genus of compounds is not sufficient to satisfy the written description requirement as to particular species or subgenuses."; see also *In re Ruschig*, 379 F.2d 990, 994-95, 154 USPQ 118, 122 (CCPA 1967) wherein the Court held that a broad generic disclosure failed to constitute a description of more narrowly claimed subject matter; see also *Fields v. Conover*, 443 F.2d 1386, 1391, 170 USPQ 276, 280 (CCPA 1971) wherein the Court stated that direction must be expressed in "full, clear, concise, and exact" language; see also *In re Ahlbrecht*, 435 F.2d 908, 911, 168 USPQ 293, 296 (CCPA 1971)). Here, the Examiner can find no such "blaze marks" or "full, clear, concise, and exact" language that would direct a person of skill in the art to the currently claimed subgenus of "disease causing" substances. For example, provisional application 60/175,047 upon which priority is claimed provides support only for producing and screening "drug" polymorphs and determining conditions that influence their solubility, delivery, bioavailability, etc. (i.e., the application is drawn to optimizing polymorphic forms of drugs). Although, "hydroxyapatite" is mentioned in the background section of this provisional application, which might reasonably be construed as a "disease causing" substance, the

specification never states that this is a substance that is going to be screened. The specification only mentions hydroxyapatite as a historical reference point stating that it is a "classic example" of crystallization. Likewise, the CIP applications and other related provisional applications are also drawn to screening "drug" polymorphs instead of "disease causing" substances and thus are also deficient (e.g., see PCT/US01/00531, section 4.3.1).

In further support of this position, the Examiner notes that Applicants' preferred species of disease causing substances are also missing from the CIP applications and their relation provisional applications. For example, the priority documents do not provide adequate support for calcium pyrophosphate, brushite, apatite, hydroxyapatite, calcium oxalate, kidney stone, bone tissue, magnesium ammonium phosphate, uric acid, gall stone, collagen, bilirubin, etc. (e.g., compare to claim 106 of the present application). In addition, the priority documents in question do not provide a definition for disease causing substance (e.g., compare to specification, page 25, paragraph labeled 145). Finally, a lack of support is also noted for the use of "shock waves" (e.g., compare to claim 101 of the present application).

Therefore the filing date of the instant application is deemed to be the filing date of 60/253,629, which is **November 28, 2000**.

Withdrawn Objections/Rejections

8. The objections to claims 46-47 are withdrawn in view of Applicants' cancellation of said claims. The rejections under 35 U.S.C. 112, second paragraph are withdrawn in view of Applicants arguments and/or amendments. The Hol et al. and Leskovar et al. rejections under 35 U.S.C. § 102 are withdrawn in view of Applicants' arguments and/or amendments. All other rejections are maintained and the arguments are addressed below.

<u>Outstanding Objections and/or Rejections</u>

Claims Rejections - 35 U.S.C. 102

9. Claims 81-131, 142 and 150 are rejected under 35 U.S.C. 102(e) as being anticipated by Levinson et al. (WO 01/51919) (of record).

For ***claim 81***, Levinson et al. (see entire document) disclose method steps for the high-throughput formation, identification, and analysis of diverse solid-forms (see Levinson et al., abstract), which anticipates the claimed invention. For example, Levinson et al. disclose producing an array of at least 96 samples (e.g., see Levinson et al., claims 19, "The array … comprising … <u>96 samples</u>"; see also page 10, lines 15-31; see also claims 22, 39, 60, 104, 118, 128, 141 and 153; see also abstract). Furthermore, Levinson et al. disclose preparing such an array in tubes and support plates or in sample well pates (e.g., see page 40, section 6.2, paragraph 1, "The array can be prepared … [by] adding the compound-of-interest and components to a plurality of sample sites, such as <u>sample wells</u> or <u>sample tubes</u> on a <u>sample plate</u>"; see also section 6.4 wherein a microtiter plate is disclosed). Levinson et al. also disclose an array that differs by (1) the amount or concentration of the disease-causing substance, (2) an identity of one or more additional components or (3) an amount or concentration of one or more of the additional components (e.g., see claim 6, "The array of claim 2, wherein one or more samples differ from one or more other samples with respect to at least one of: (a) amount or concentration of the compound-of-interest … (c) the identity of one or more of the components"; see also claims 26, 43, 65, 91, 108, 132, 145 and 159). Levinson et al. also

disclose processing one or more of the samples to induce crystallization, precipitation or deposition of the disease causing substance (e.g., see Levinson et al., page 65, line 29 wherein Levinson et al. disclose "amyloid" as a disease causing substance, presumably screening said amyloid for Alzheimer's disease wherein the physical state is "induced"; see also section 4.4.1, page 24, line 27 wherein "calcium phosphate" is disclosed as an "excipient", but also falls within the scope of a disease causing substance, compare to claim 106); see also section 6.7 wherein the excipient concentration is varied; see also page 45, lines 6-8; see especially page 70, section 6.9 entitled, "Arrays to Identify Conditions, Compounds, or Compositions That Prevent or Inhibit Crystallization, Precipitation, Formation, or Deposition of Solid Forms"; see also section 2.1.1., especially page 2, lines 5-12, "Common parameters that can be controlled to promote or discourage precipitation or crystallization include … adjusting the amount or the concentration of a component; component identity (adding one or more additional components). In addition, Levinson et al. disclose "analyzing" the array and "selecting" those processed samples that exhibit inhibition or prevention of a physical state (e.g., see page 70, section 6.9; see also section 6.4; see also claims 26(b)/(e), 43(b)/(e), 65(b)/(e), 91(b)/(e), 108(d) and 132(d); see also page 29, line 15; see also Levinson et al., claims 39(c), 46-47, 60(b), 104(c); see also figure 1; see also page 71, paragraph 1).

For ***claims 82-83***, Levinson et al. disclose solids, liquids and dissolved forms (e.g., see Levinson et al., page 33, section 4.8 on physical states).

For ***claim 84***, Levinson et al. disclose heating said samples in a sample incubation module to a temperature T1, analyzing said samples for the presence of undissolved

solids using visual analysis, and cooling said samples to a final temperature T2 (e.g., see page 60, lines 15-21, "In one example of use of the incubation chamber, the sample plates can be heated to a temperature (Tl) ...After the heating treatment, the plates can be subjected to a cooling treatment to a final temperature T2").

For ***claims 85-88***, Levinson et al. disclose a support plate with glass tubes and a cap that can be pierced with a needle (e.g., see page 14, last paragraph, "In this embodiment, the array consists of 96 individual glass tubes in a metal support plate ... The sealing is accomplished by capping with a plug-type cap ... Specifically, the plunger cap is pierced with a standard syringe needle and fluid").

For ***claim 89***, Levinson et al. disclose 1000 samples (e.g., see claims 20, 21, 37, 58, 102).

For ***claim 90***, Levinson et al. disclose the generation of a work list (e.g., see page 38, lines 23-24, "From the spread sheet, a work list can be generated for instructing the automated distribution mechanism to prepare an array of samples according to the various combinations generated by the formulating software").

For ***claims 91 and 121-123***, Levinson et al. disclose less than one milligram (e.g., see claims 4-5).

For ***claim 92***, Levinson et al. disclose aspiration (e.g., see page 14, line 28).

For ***claim 93***, Levinson et al. disclose polarized light filters (e.g., see page 47, last paragraph).

For ***claim 94***, Levinson et al. disclose small molecules as components (e.g., see section 6.3.5, "... a component can be ... small molecules"; see also section 6.7).

For ***claims 95-96***, Levinson et al. disclose the use of at least 1 sub-array with at least 24 samples (e.g., see section 4.1, "An array can comprise one or more groups of samples also known as sub-arrays. For example, a group can be a 96-tube plate of sample tubes or a 96-well plate of sample wells in an array consisting of 100 or more plates").

For ***claims 97-100***, Levinson et al. disclose "process[ing] … by adjusting the value of the temperature; adjusting the time of incubation; adjusting the pH; adjusting the amount or the concentration of the compound-of-interest; adjusting the amount or the concentration of one or more of the components adding one or more additional components nucleation (e.g., an optically pure seed crystal to induce preferential crystallization) or controlling the evaporation of one or more of the components, such as the solvent (e.g., adjusting a value of pressure or adjusting the evaporative surface area) or a combination thereof: (e.g., see page 70, paragraph 1). Levinson et al. also disclose the use of ultrasound (e.g., see

For ***claim 101***, Levinson et al. disclose, for example, ultrasound (e.g., see page 60, line 25, "Nucleation events include mechanical stimulation, and exposure to sources of energy, such as acoustic (ultrasound), electrical, or laser energy").

For ***claims 102-105, 111-120, 126-128***, Levinson et al. disclose adjusting various processing parameters (e.g., see section 2.1.1; see also section 4.5, "As used herein, the term "processing parameters" means the physical or chemical conditions under which a sample is subjected and the time during which the sample is subjected to such conditions. Processing parameters include, but are not limited to, adjusting the temperature adjusting

the time adjusting the pH adjusting the amount or the concentration of the compound-of-interest adjusting the amount or the concentration of a component identity (adding one or more additional components) adjusting the solvent removal rate introducing of a nucleation event introducing of a precipitation event controlling evaporation of the solvent (e. g., adjusting a value of pressure or adjusting the evaporative surface area) and adjusting the solvent composition"; see also section 6.9, see also "For example, samples can have one or more of the following components at various concentrations: excipients; solvents; salts; acids; bases; gases"; see also section 4.1).

For ***claims 106 and 120***, Levinson et al. disclose calcium phosphate and amyloid (e.g., see e.g., see Levinson et al., page 65, line 29 wherein Levinson et al. disclose "amyloid" as a disease causing substance, presumably screening said amyloid for Alzheimer's disease wherein the physical state is "induced"; see also section 4.4.1, page 24, line 27 wherein "calcium phosphate" is disclosed as an "excipient", but also falls within the scope of a disease causing substance, compare to claim 106. Please note that calcium phosphate has a molecular weight less than about 1000 g/mol.

For ***claim 107***, Levinson et al. disclose detecting the presence and/or absence of a solid (e.g., see Levinson et al., section 4.2, "As used herein, the term "sample" means a mixture of a compound-of-interest and one or more additional components to be subjected to various processing parameters and then screened to detect the presence or absence of solid-forms").

For ***claim 108***, Levinson et al. disclose determining if the solid is amorphous or crystalline (e.g., page 37, lines 6-7, "Whether the detected solid is crystalline or amorphous can then be determined").

For ***claims 109-110***, Levinson et al. disclose screening 1000 samples per day (e.g., see Levinson et al., claims 37, 58, 102, etc.).

For ***claims 124-125***, Levinson et al. disclose 10-200 μl (e.g., see section 4.2, "Preferably, the sample has a total volume of 100-250 μl").

For ***claims 129-131***, Levinson et al. disclose various parameters for contollling crystal nucleation and growth (e.g., see section 6.3.4, "Supersaturation is the thermodynamic driving force for both crystal nucleation and growth ... [which] can be controlled by temperature and the amounts or concentrations of the compound-of-interest and other components").

For ***claims 142 and 150***, Levinson et al. disclose Raman spectroscopy and an in vitro assay (e.g., see claims 46, 70, 71, 126 and 127).

Response

10. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "Levinson et al. is not available as prior art in view of the corrected priority/benefit claim" (e.g., see 3/4/04 Response, page 15, paragraph 4).

This is not found persuasive for the following reasons:

The Examiner contends that Applicants have not been afforded priority/benefit to Levinson (see priority section above) and, as a result, Applicants' arguments are moot.

Accordingly, the 35 U.S.C. § 102 rejection cited above is hereby maintained.

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 81-131, 142 and 150 are rejected under 35 U.S.C. 103(a) as being unpatentable over Selengut et al. (U.S. Patent No. 5,776,348) (Date of Patent is July 7, 1998) and Klein et al. (Klein, J.; Lehmann, C. W.; Schmidt, H.-W.; Maier, W. F. "Combinatorial Material Libraries on

the Microgram Scale with an Example of Hydrothermal Synthesis" *Angew. Chem. Int. Ed.* **1998**, *37(24)*, 3369-3372) and Jandeleit et al. (Jandeleit, B.; Schaefer, D. J.; Powers, T. S.; Turner, H.W.; Weinberg, W. H. "Combinatorial Materials Science and Catalysis" *Angew. Chem. Int. Ed.* **1999** *38*, 2494-2532) and Emiabata-Smith et al. (Emiabata-Smith, D. F., Crookes, D. L.; Owen, M.R. "A practical approach to accelerated process screening and optimization" *Organic Process Research & Development* **1999**, *3*, 281-288) and Findlay et al. (Findlay, W. P.; Bugay, D. E. "Utilization of Fourier transform-Raman spectroscopy for the study of pharmaceutical crystal forms" *Journal of Pharmaceutical and Biomedical Analysis* **1998**, *16*, 921-930) (IDS, RD).

For ***claims 81 and 94***, Selengut et al. (see entire document) teach a method for the "identification of compounds that affect mineral precipitation" (see abstract), which reads on the claimed invention. For example, Selengut et al. disclose screening method for identifying conditions, compounds or compositions that inhibit or prevent transitions of physical state (e.g., see column 2, lines 49-65, "The present invention also relates to the identification of a factor that inhibits the formation of mineral precipitates ..."; see also Examples 1-4). In addition, Selengut et al. dispensing a "disease-causing" substance in liquid or dissolved form with an automatic distribution mechanism (e.g., see paragraph bridging columns 2-3, "The present invention provides a method for inhibiting formation of a mineral precipitate in a solution ... the growth of struvite precipitates ... calcium phosphate mineral particles ... is inhibited"; see also Examples 1-4; see also column 4, lines 34-43). In this scenario, the "disease" is, for example, kidney stones and the corresponding "disease-causing" substances are the struvite precipitates, calcium phosphate mineral particles, etc. (see also Applicants' specification, page 25, paragraph

145, wherein disease causing substance is defined to include kidney stones). In addition, Selengut et al. disclose (1) changing the amount or concentration of the disease-causing substance, (2) the identity of one or more of the additional components and (3) the amount or concentration of one or more additional components (e.g., see Example 1, especially column 11, paragraphs 1-2, "other artificial urine systems [disease-causing substances] can be prepared ... "; see also column 4, lines 34-43, "... the invention provides a method for identifying compounds that alter the rate ... of mineral precipitate formation in a solution [by] ... (b) <u>contacting the solution with a test compound</u> [i.e., an additional component] ..."; see also Examples 2-4). Selengut et al. disclose processing one or more of the samples to induce crystallization, precipitation or deposition of the disease causing substance (e.g., see Example 1 wherein the addition of urease is disclosed, "Urease splits urea molecules into ammonia and carbonate, thereby alkalinizing the solution and <u>inducing crystallization</u> of struvite and/or calcium phosphate minerals"). Selengut also disclose analyzing the processed samples to detect the induction of said crystallization (e.g., see column 4, lines 34-43, "Additionally, the invention provides a method for identifying compounds that alter the rate or extent of mineral precipitate formation in a solution, comprising ... (c) <u>detecting</u> a difference between the rate or extent of <u>mineral precipitate formation</u> in the presence of the compound and the rate or extent of mineral precipitate formation in the absence of the compound", see also Examples 1-4). Finally, Selengut disclose selecting those processed samples that exhibit inhibition or prevention of transition in physical state (e.g., see Example 1, "Samples of the artificial urine system of the present invention can be

removed [i.e., selected] at any time for analysis ... Available methods for analysis of initiation time, aggregation, crystal size, and/or surface charge include, for example, those described by Hess et al. ..."; see also Examples 2-4).

For ***claims 82-83***, Selengut et al. disclose the use of a solution or dissolved form (e.g., see paragraph bridging columns 2-3, "The present invention provides a method for inhibiting formation of a mineral precipitate in a solution ... the growth of struvite precipitates ... calcium phosphate mineral particles ... is inhibited"; see also Examples 1-4; see also column 4, lines 34-43).

For ***claim 84***, Selengut et al. disclose the use of processing samples by heating said samples in an sample incubation to a temperature T1, analyzing said sample for the presence of undissolved solids and cooling said samples to a final temperature T2 (e.g., see Selengut et al., example 2).

For ***claim 92***, Selengut et al. disclose aspiration (e.g., see Example 3).

For ***claim 93***, Selengut et al. disclose polarization microscopy (e.g., see Example 1).

For ***claims 97-100, 102-1-5, 111-120, 126-128, 129-131***, Selengut et al. teach the use of many different processing parameters (e.g., see Example 1, "The artificial urine system of the present invention is manipulable so that precipitate formation proceeds for different lengths of time, and/or occurs under different conditions (e.g. different pH, temperature, pressure, viscosity, and/or agitation; in the presence of different minerals, proteins, and/or other potential stone components; with or without the exchange of gases with the environment; etc.) ... Samples of the artificial urine system of the present

invention can be removed at any time for analysis of, for example, (i) the time of initiation of precipitation and/or of crystal nucleation; (ii) the rate and/or extent of particle aggregation; and/or (iii) the chemical composition, protein content, size, size distribution, surface charge, morphology, and/or adhesion properties"; see also Example 2).

For ***claim 101***, Selengut et al. teach the use of mechanical agitation (e.g., see example 1, "The artificial urine system of the present invention is manipulable so that precipitate formation proceeds for different lengths of time, and/or occurs under different conditions (e.g. different pH, temperature, pressure, viscosity, and/or agitation ...").

For ***claim 106 and 120***, Selengut et al. teach many disease causing substances such as struvite, calcium phosphate, kidney stones, etc. that have molecular weights <1000 and thus are considered "small molecules" (e.g., see paragraph bridging columns 2-3, "The present invention provides a method for inhibiting formation of a mineral precipitate in a solution ... the growth of struvite precipitates ... calcium phosphate mineral particles ... is inhibited"; see also Examples 1-4; see also column 4, lines 34-43). In this scenario, the "disease" is, for example, kidney stones and the corresponding "disease-causing" substances are the struvite precipitates, calcium phosphate mineral particles, etc. (see also Applicants' specification, page 25, paragraph 145, wherein disease causing substance is defined to include kidney stones).

For ***claims 107-108***, Selengut et al. teach analyzing samples for the presence or absence of a solid using a spectrophotometer (e.g., see Examples, especially example 1, "Available methods for analysis of initiation time, aggregation, crystal size, and/or

surface charge include, for example, those described by Hess et al ... For example, turbidity of the solution, which reflects the number of particles in the solution but is not significantly influenced by the size of those particles, can be monitored by spectrophotometry, preferably in real-time so that both the initiation of precipitation and/or crystal nucleation and the rate and extent of particle aggregation can be monitored.").

For ***claims 124-125***, Selengut et al. disclose the use of "µL" volumes (e.g., see Examples 2, 3, 4 and 6).

For ***claim 150***, Selengut et al. teach an ELISA in vitro assay (e.g., see Examples 1 and 6; see also figure 2).

<u>The prior art teachings of Selengut et al. differ from the claimed invention as follows</u>:

For ***claim 81***, Selengut et al. are deficient in that they do not specifically teach the use screening "at least 96 samples" in tubes and support plates or in sample well plates. Selengut et al. disclose multiple samples (e.g., see Examples), but do not indicate the total number of samples tested on a given support plate.

For ***claim 85-87***, Selengut et al. are deficient in that they do not teach the use of glass sample tubes with caps in a support plate.

For ***claim 89***, Selengut et al. are deficient in that they do not disclose at least 1000 samples.

For ***claim 90***, Selengut et al. are deficient in that they do not describe the generation of a work list for instructing an automated distribution mechanism to prepare said arrays.

For ***claim 91 and 121-123***, Selengut et al. are deficient in that they do not teach nanogram scale.

For ***claim 95-96***, Selengut et al. are deficient in that they do not teach the use of a sub-array.

For ***claims 142 and 150***, Levinson et al. are deficient in that they do not disclose the use of Raman spectroscopy in an in vitro assay.

<u>However, the combined references of Klein et al., Jandeleit et al., Findlay et al. and Emiabata-Smith et al. teach the following limitations that are deficient in Selengut et al.</u>:

For ***claim 81***, the combined references of Klein et al. (see entire document), Jandeleit et al. (see entire document) and Emiabata-Smith et al. teach, for example, the use of a multireactor plate for the combinatorial screening of material libraries that include at least "100 chambers" for screening wherein the samples are automatically dispensed into the chambers (e.g., see figures 1-2; see also page 3370, column 1, lines 1-2, "... provide about 100 chambers"; see also lines 6-7, "... amounts [dispensed] ... by a microliter pipette or a <u>robot</u>"). See also case studies shown for Emiabata-Smith (e.g., see Emiabata-Smith, figure 4).

For ***claims 85-88***, the combined references of Klein et al., Jandeleit et al., Findlay et al. and Emiabata-Smith et al. teach many different variations of support plates/glass

holders that were routinely used (and commercially available) in combinatorial synthesis (e.g., see Jandeleit et al., section 5.1.3. wherein an aluminum plate with cylindrical glass vials is disclosed). See also Emiabata-Smith wherein the use of a syringe is disclosed (e.g., see page 283, column 2, last paragraph; see also page 285, column 1, step 1)

For ***claims 89 and 109-110***, the combined references of Klein et al., Jandeleit et al., Findlay et al. and Emiabata-Smith et al. teach at least 1000 samples (e.g., see Jandeleit et al., page 2500, column 1, second to last paragraph, "Xiang and Schultz have demonstrated that a scanning multihead inkjet delivery system can be used to perform automated micro-synthesis of solid-state material libraries ... <u>Droplets are delivered sequentially to single reaction wells</u>; the droplet size is on the order of 500 picoliters with reproducibility better than 99% and a maximum delivery speed of <u>2000 droplets per second</u>").

For ***claim 90***, the combined references of Klein et al., Jandeleit et al., Findlay et al. and Emiabata-Smith et al. teach that work lists were routinely used in automated procedures (e.g., see Jandeleit et al., page 2508, column 1, paragraph 1, "The preparation of the MIPs was automatically performed by using programmed liquid handling equipment"; see also Emiabata-Smith et al., figures 6-8).

For ***claim 91 and 121-123***, the combined references of Klein et al., Jandeleit et al., Findlay et al. and Emiabata-Smith et al. teach microgram and nanogram scale (e.g., see Klein et al., title, "Combinatorial Material Libraries on the <u>Microgram</u> Scale with an Example of Hydrothermal Synthesis"; see also Jandeleit et al., page 2500, column 1, second to last paragraph, "Xiang and Schultz have demonstrated that a scanning

multihead inkjet delivery system can be used to perform automated micro-synthesis of solid-state material libraries, which enables rapid delivery and accurate control of nanoliter deposition volumes").

For **claim 92**, the combined references of Klein et al., Jandeleit et al., Findlay et al. and Emiabata-Smith et al. teach aspiration (e.g., see Emiabata-Smith et al., page 285, step 1, "The operator first defines … the aspiration rate").

For ***claim 95-96***, the combined references of Klein et al., Jandeleit et al., Findlay et al. and Emiabata-Smith et al. teach the use of sub-libraries (e.g., see Jandeleit et al., column 2, last full paragraph).

For ***claim 97-100, 102-1-5, 111-120, 126-128***, the combined references of Klein et al., Jandeleit et al., Findlay et al. and Emiabata-Smith et al. teach the use of adjusting various processing parameters (e.g., see Emiabata-Smith et al., page 282, "Applications Scope" section, "Process optimisation: determining the levels of continuous variables such as temperature, reagent concentration, time to optimise yield, purity, cost, etc."; see also Jandeleit et al., Introduction, "combinatorial chemistry and high-throughput screening and represent a powerful research strategy when applied to problems where a large parameter space").

For ***claim 101***, the combined references of Klein et al., Jandeleit et al., Findlay et al. and Emiabata-Smith et al. teach the use of mechanical stimulation (e.g., see Emiabata-Smith et al., page 283, last full paragraph, "A number of types of magnetic stirrer bar have been investigated as the degree of agitation required for different chemistries varies.").

For ***claims 107-108***, the combined references of Klein et al., Jandeleit et al., Findlay et al. and Emiabata-Smith et al. teach the use detecting the presence and/or absence of a solid including amorphous versus crystalline entities (e.g., see Klein et al., page 3370, column 1, last paragraph, "The only information expected was crystalline or amorphous with a qualitative indication of the class of materials that had been formed").

For ***claims 124-125***, the combined references of Klein et al., Jandeleit et al., Findlay et al. and Emiabata-Smith et al. teach the use "μl" volumes (e.g., see Klein et al., page 3370, column 1, paragraph 1, "The reaction mixtures are dosed in amounts of up to 2 mL by a microliter pipette or a robot"; see also Emiabata-Smith et al., page 284, last paragraph).

For ***claims 142***, the combined references of Klein et al., Jandeleit et al., Findlay et al. and Emiabata-Smith et al. teach the use of Raman spectroscopy (e.g., see Jandeleit et al., page 2500, column 1, last paragraph; see also Findlay et al., abstract and title).

It would have been obvious to one skilled in the art at the time the invention was made to screen compounds that inhibit mineral precipitation as taught by Selengut et al. using the high-throughput screening apparatus and/or techniques as disclosed by Klein et al., Jandeleit et al., Findlay et al. and Emiabata-Smith et al. because Klein et al., for example, teach that their apparatus is useful for characterizing precipitates and/or crystals (e.g., see Klein et al., page 3372, column 1, paragraph 3, "In general, every solid synthesis in liquid phase under pressure and temperature should be possible. Such a reactor should be ideal for the combinatorial screening of new microcrystalline or amorphous solids), which would encompass the precipitates and/or crystals disclosed by

Selengut et al. Furthermore, one of ordinary skill in the art would have been motivated to use the techniques as taught by Klein et al. because according to Klein et al. their techniques are "... ideal for screening microcrystalline or amorphous solids, especially since the reactor bottom can be exchanges and libraries can be prepared directly on the substrate of choice" (e.g., see Klein et al., page 3372, column 1, last paragraph; see also page 3369, column 2, last paragraph wherein other advantages like "smaller reaction volumes", the use of "X-ray diffraction" directly on the substrate are disclosed; see also page 3372, column 1, paragraph 2 wherein "increased efficiency" via automatization is disclosed). Furthermore, a person of skill in the art would generally have been motivated to automate any material library including the libraries disclosed by Selengut et al. because according to Jandeleit et al., "... with these new [combinatorial] technologies come the promise of faster commercialization rates and reduced research and development costs ... [because] combinatorial process aims at efficiently exploring the large parameters space that controls properties of a product through the combination of rapid parallel or combinatorial synthesis of vast number of compounds and subsequent high-throughput assaying of these compounds for any given application ... by combinatorialy varying process and reaction conditions ... the total number of experiments one can screen rises exponentially, which drastically increases the chances of identifying a new material" (e.g., see Jandeleit et al., abstract). Thus, the use of combinatorial high throughput screening as exemplified by Jandeleit et al. and Klein et al. is unquestionably ideal for exploring the large number of process variables, reaction conditions, and samples disclosed by Selengut et al. Furthermore, a person of skill in the

art would have been motivated to use Raman spectroscopy to analyze the sample disclosed by Selengut because Findlay et al. indicates that this technique is ideal for analyzing crystal forms (e.g., Findlay et al., abstract; see also conclusions on page 929-930 wherein enhanced characterization via qualitative and semi-qualitative analysis is disclosed). Finally, one of ordinary skill in the art would have reasonably expected to be successful because Klein et al. teach several successful examples of measuring crystallinity as would be required by the method steps of Selengut et al. (e.g., see Klein et al., figure 2) and Klein et al. explicitly state that this methodology could be extended to all solid samples (e.g., see page 3372, column 1, paragraph 3, "In general, <u>every solid synthesis</u> ... should be possible. Such a reactor should be ideal for the combinatorial screening of new microcrystalline or amorphous solids"; see also Jandeleit et al, abstract, wherein the authors indicate that combinatorial chemistry is broadly applied to all fields of chemistry, "it is not surprising that a similar paradigm is taking hold in the chemical industry as a whole"; see also conclusion, "A common underlying theme associated with these technologies is miniaturization, parallelization, and automation so that large numbers of samples can be synthesized and screened efficiently").

In addition, the Examiner notes that with respect to the number of samples prepared (e.g., at least 96), this would also be obvious to one of ordinary skill based on the fact that when "the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA1955). Also note that optimization of process steps, especially with respect to ordering, is within the routine skill of the art.

In re Burhans, 154 F.2d 690, 69 USPQ330 (CCPA 1946) (selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results). With respect to the repetition of steps (i.e. number of samples analyzed, for example, at least 96), see *In re Harza*, (274 F.2d 669, 124 USPQ 378 (CCPA 1960)) where the court held that mere duplication of parts has no patentable significance unless a new and unexpected result is produced.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.

March 10, 2005